EXHIBIT A
Application Serial No. 09/089,871

Application No.: 09/089,871 Docket No.: 251502008600

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Rudolf C. BARENDSE et al.

Application No.: 09/089,871 Confirmation No.: 3289

Filed: June 4, 1998 Art Unit: 1652

For: HIGH-ACTIVITY PHYTASE COMPOSITIONS Examiner: Delia M. Ramirez, Ph.D.

DECLARATION UNDER 37 C.F.R. § 1.132

MS Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Madam:

1. I, Dr. Lutz End, am an expert in the field of chemical and pharmaceutical formulation, and was at the time of the invention. I am presently employed as Head of Formulation and Nutrition R&D in the Care Chemicals Division at BASF SE (formerly known as the Fine Chemicals Division of BASF Aktiengesellschaft). My resume is attached as documentation of my credentials (**Exhibit A**).

2. This Declaration is being filed in response to the Examiner's concerns regarding the meaning of the term "increased pelleting stability" that were raised in the Office Action dated July 27, 2007 ("the OA"). First, the Examiner expressed concern that the term is "unclear and confusing in the absence of a basis for comparison (i.e., increased with respect to what)" (the OA at p. 3, ¶ 4). Second, the Examiner seems to believe that a person skilled in the art at the time of the invention "would interpret the term 'pelleting stability' to refer to the structural stability of the pellet under different conditions (e.g., temperature, pressure, pH, etc.)" (Id.) It appears from the Office Action that the Examiner did not understand the technical disclosure in Example 5 of the specification and consequently could not determine the intended meaning of the term "pelleting stability."

3. I hereby declare that the skilled artisan, at the time of the invention, using the teachings of the specification and the knowledge known to the skilled artisan, would have understood that the term "pelleting stability" was intended to refer to residual phytase activity in the pellet after the pelleting process, and not to the structural stability of the pellet itself.

4. To illustrate the state of the art at the time of the invention, the Examiner is first referred to the text of the instant specification as published (US 2002/0034798 A1), specifically to Example 5 entitled "High Activity Phytase Stability Tests" on pages 7-8 (paras. **[0114] – [0127]**).

5. The preamble of Example 5 clearly states that "[t]o demonstrate that a higher enzyme concentration (in granules made using the high activity phytase liquid) gives a higher pelleting stability, granulates with an increasing enzyme concentration were made and the pelleting stability of these samples were tested" (para. **[0115]**).

6. The descriptions of Comparative Samples A, B, C indicate that the three enzyme granulates had pre-pelleting phytase activities of 610 FTU/g, 4170 FTU/g and 6830 FTU/g, respectively (see paras. **[0116] - [0124]**).

7. The final section of Example 5 is entitled "Comparison of pelleting stabilities." The section states that the enzyme granulates A, B and C were mixed with a feed premix at different mixing ratios, pre-treated by steam injection to give a temperature rise to 75°C, after which the mixtures were pelleted in a pelleting machine to obtain the feed pellets at a temperature of 82°C, which were subsequently dried. The section further explains that this process is typical for the feed industry to obtain feed pellets (see para. **[0126]**).

8. After the pellets were dried, the enzyme activity was measured again (data not shown), and the post-pelleting yield was calculated by comparing the residual phytase activity of each sample with corresponding pre-pelleting activity adjusted for the different mixing ratios with the feed premix. The resulting post pelleting phytase activity yields are summarized in Table 2, which shows that the low-phytase Comparative Sample A had a less than 17% yield, whereas the high-phytase Comparative Samples B and C had significantly higher yields of 37% and 48%,

respectively. Accordingly, Applicants conclude that "the two granules with the highest enzyme concentration had much higher pelleting stability" (para. **[0127]**).

9. It is important to note that structural stability of the pellets is not discussed at all in Example 5, whereas all of the discussion focuses exclusively on phytase activity. Therefore, the only reasonable conclusion that could have been made by a skilled artisan at the time of the invention is that the higher pelleting stability contemplated by the present invention means a higher yield of residual phytase activity after pelleting, and not higher structural stability of the pellets.

10. To further illustrate the state of the art at the time of the invention, the Examiner is next referred to several prior art references discussing issues relating to pelleting stability.

11. The problem of post-pelleting phytase performance was recognized as early as 1990, when Simons wrote:

> "The pelleting experiments with feed to which microbial phytase had been added showed significant inactivation of phytase activity when temperatures of the pellets after pelleting exceeded 84° C..." P.C.M. Simons, et al., Improvement of Phosphorus Availability by Microbial Phytase in Broilers and Pigs, *Br. J. Nutr.* 1990, 64:525-540, at p.537 (**Exhibit B**).

12. In 1993, Cowan referred to enzyme stability in the context of feed pelleting:

> "At a pre-pelleting conditioning temperature of 65° C, a commercial enzyme absorbed to its carrier is completely *stable*. However, as the conditioning temperature increases, the enzyme is inactivated until at 75° C the residual activity is about 30% of the starting level." W.D. Cowan, The Stability of Enzymes in Animal Feeds, *Feed Intl.* 1993, 14(4):22-25, at p. 23 (**Exhibit C**).

13. In the same year, Gadient also remarked that:

> "hydrothermal processes, such as pelleting, extrusion and expansion, have been recognized as potentially destructive for... phytase." M. Gadient, et al., Experiences with Enzymes in Feed Manufacturing, *in Proc. 1st Symp. on Enzymes in Animal Nutrition*, Kartause Ittingen, Switzerland, Oct. 13-16, 1993, 255-262, at p. 255 (**Exhibit D**).

14. Similarly, in 1993 Nunes wrote:

"The resistance of endogenous phytase and eventually that of the added one to the pelleting temperature appeared as an important question... It appeared that steam-pelleting at temperatures higher that 60° C strongly reduced phytase activity. This was particularly marked for temperatures higher than 75° C. When pelleting at 80° C the recovered phytase activity represented about 50% of the endogenous one demonstrating inactivation of both enzymatic activities... Thus, with the aim of phytase preservation in pig feed technological precautions should be taken when using steam-pelleting." C.S. Nunes, Evaluation of Phytase Resistance in Swine Diets to Different Pelleting Temperatures, *in Proc. 1st Symp. on Enzymes in Animal Nutrition*, Kartause Ittingen, Switzerland, Oct. 13-16, 1993, 269-271 **(Exhibit E)**.

15. Consistent with the earlier reports, in 1995 Ravindran noted:

"High temperatures employed during ingredient processing or during pelleting of diets can also influence the native phytase activity of plant ingredients. Plant phytase activity is not altered by such treatments at temperatures between 47° and 62° C, but higher temperatures (70-80° C) can cause partial or total inactivation." V. Ravindran, et al., Phytates: Occurrence, Bioavailability and Implications in Poultry Nutrition, *Poult. Avian Biol. Rev.* 1995, 6(2):125-143, at p. 129 **(Exhibit F)**.

16. In 1997, Spring used the term "stability curve" in the context of feed pelleting:

"Enzymes are susceptible to hydrothermal treatments as applied in pelleting, expansion and extrusion. It appears that each enzyme product has a specific '*stability curve*' and a critical temperature point at which enzyme losses start to accelerate." W.G. Spring, et al., Application of Enzymes in Compound Feeds, *CIHEAM – Options Mediterraneennes* 1997, 26:175-179, at p. 176 **(Exhibit G)**.

17. In 1997, Esteve-Garcia also wrote about enzyme stability during pelleting:

"*Stability* of enzymes during the pelleting process has been a cause for concern." E. Esteve-Garcia, et al., Bioefficacy of Enzyme Preparations Containing β-Glucanase and Xylanase Activities in Broiler Diets Based on Barley or Wheat, in Combination with Flavomycin, *Poult. Sci.* 1997, 76:1728-1737, at p. 1728 **(Exhibit H)**.

18. Finally, in 1998, the year of the present invention, Wyss specifically used the term "pelleting stability":

> "Enzymes that are used in animal feed supplements should be able to withstand temperatures of 60° to 90° C, which may be reached during the feed pelleting process... These findings confirm that *A. niger* pH 2.5 acid phosphatase is irreversibly inactivated at temperatures above 80° C and that the capacity of *A. fumigatus* phytase to refold properly after heat denaturation may favorably affect its *pelleting stability*." M. Wyss, et al., Comparison of the Thermostability Properties of Three Acid Phosphatases from Molds: *Aspergillus fumigatus* Phytase, *A. niger* Phytase, and *A. niger* pH 2.5 Acid Phosphatase, *Appl. Envir. Microbiol.* 1998, 64(11):4446-4451, at p. 4446, abstract; see also p. 4450 (**Exhibit I**).

19. Thus, based on the prior art literature, there is a clear sense that each enzyme has its own pattern of thermal inactivation as a result of feed pelleting, also known as a "stability curve". Any modifications to the enzyme itself and/or to the process of granulation that have a tendency to shift the stability curve to the right, i.e., toward a higher temperature tolerance, would be understood by a skilled artisan to result in an "increased pelleting stability" as recited in claims 18 and 19 of the present application.

20. Accordingly, based on the teachings of the specification and the knowledge and methods known at the time of the invention, the skilled artisan would have appreciated that the term "increased pelleting stability" was intended to refer to a higher than normal post-pelleting phytase activity in the pellet, and not to the structural stability of the pellet itself.

21. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Respectfully submitted,

Dated: January 22, 2008

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To Whom It May Concern:

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Curriculum Vitae Dr. Lutz End

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Married to Anke, Emmy Grethe Lisa Wilhelmiene End, geb. Seibel
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Education:
1964-1976
Massbruchschule Lage/Lippe
Engelbert-Kaempfer-Gymnasium Lemgo
1976 Abitur

1976-1977
Military Services

1977-1984
Studies in chemistry at the University of Bielefeld, Germany
1984 Diploma in Chemistry

1984-1988
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Professional Carrier:
1988 Start at BASF Aktiengesellschaft
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